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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/886,011	06/22/2001	Peter Virgil Fisher	07414.0040-00000	4801

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EXAMINER	
RILEY, JEZIA	

ART UNIT	PAPER NUMBER
1637	10

DATE MAILED: 01 31 2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/886,011	FISHER ET AL.	
	Examiner	Art Unit	
	Jezia Riley	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-123* is/are pending in the application.

4a) Of the above claim(s) *1-100 and 115-123* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *101-114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-123* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group IX (Claims 101-114) in Paper No. 9 is acknowledged.

Oath/Declaration

2. It does not state that the person making the oath or declaration has reviewed and understands the contents of the specification, including the claims, as amended by any amendment specifically referred to in the oath or declaration.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 101-114 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 101-114 are vague and indefinite because it is unclear of what is exactly the dye-labeled ribonucleotide of the invention. It is suggested that clarification such as for example" dye-labeled ribonucleotide of formula I, or II, ..." be added for clarification.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 101-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanton et al. (6,500,650) in view of Rosenblum (Nucleic Acids Research 1997, Vol. 25, pp. 4500-4504).

Stanton et al. relates to a method for detecting a variance in the nucleotide sequence among related polynucleotides by replacing a natural nucleotide in a polynucleotide at substantially each point of incorporation of the natural nucleotide with a modified nucleotide, cleaving the modified polynucleotide at substantially each point of incorporation of the modified nucleotide, determining the mass of the

fragments obtained and then comparing the masses with those expected from a related polynucleotide of known sequence or, if the sequence of a related polynucleotide is unknown, by repeating the above steps with a second related polynucleotide and then comparing the masses of the fragments obtained from the two related polynucleotides.

The reference relates to methods for producing and identifying polymerases with novel properties with respect to incorporation and cleavage of modified nucleotides. A modified nucleotide may contain a modified base, a modified sugar, a modified phosphate ester linkage or a combination of these. Base-modification is the chemical modification of the adenine, cytosine, guanine or thymine (or, in the case of RNA, uracil) moiety of a nucleotide such that the resulting chemical structure renders the modified nucleotide more susceptible to attack by a reagent than a nucleotide containing the unmodified base.

One approach to finding polymerases with the proper capabilities is to take advantage of the diversity inherent among naturally occurring polymerases including, without limitation, RNA polymerases, DNA polymerases and reverse transcriptases. Naturally occurring polymerases are known to have different affinities for non-natural nucleotides and it is likely that a natural polymerase, which will perform the desired incorporation, can be identified. In some cases, use of a mixture of two or more naturally occurring polymerases having different properties regarding the incorporation of one or more non-natural nucleotides may be advantageous. For example, the use of two polymerases,

an exonuclease-free N-terminal deletion mutant of Taq DNA polymerase and a thermostable DNA polymerase having 3'-exonuclease activity, to achieve improved polymerization of long DNA templates. Naturally occurring polymerases from thermophilic organisms are preferred polymerases for applications in which amplification by thermal cycling, e.g., PCR, is the most convenient way to produce modified polynucleotides.

The full-length clone can be purified after extension and prior to cleavage so that prematurely terminated fragments due to stops caused by polymerase error or template secondary structure can be removed before gel electrophoresis resulting in cleaner cleavage bands. In fact, it may not even be necessary to perform such clean up in that the prematurely terminated polymerase extension fragments themselves will be cleaved if they contain a modified nucleotide and those correctly cleavage fragments will simply augment the other fragments obtained from the cleavage of the full length clone (although such augmentation is confined to fragments shorter than the site of premature termination).

As with the other methods described at some point, a detectable label is incorporated into the system, either by use of a labeled primer, a labeled nucleotide, a labeled ribonucleotide, a labeled, modified nucleotide or a labeled, modified ribonucleotide. Furthermore, a label may be incorporated during the cleavage reaction using a labeled TCEP or a labeled secondary amine. Alternatively, a label may be incorporated after

selective hybridization has occurred, i.e. after the temperature has been raised to a degree whereby at least one of the fragments dissociates from the oligonucleotide probe. FIG. 40 demonstrates one approach to detecting polymorphisms by incorporation of labeled ribonucleotides in a DNA segment. First, PCR amplification of the region of DNA surrounding the single nucleotide polymorphism is performed in the presence of two labeled ribonucleotides, F1-rATP and F2-rGTP. In this example, F1 and F2 are different labels and thus can be differentially detected. In the example shown in the figure, there is an A or G polymorphism, which occurs downstream from primer 1. The amplified DNA segment incorporating the labeled F1-rATP and F2-rGTP is subjected to chemical cleavage at the site of incorporation of the labeled ribonucleotides to produce labeled fragments. The labeled fragments are identified in FIG. 40 as A allele-F1 and G allele-F2. The fragments are then contacted with an oligonucleotide probe under conditions amenable to hybridization. Depending on the different detectable labels, the presence of the A allele or G allele may be identified in the DNA sample. Further, a sample that has both types of alleles may appear as a hybrid signal.

FIG. 4 is the RFC mass spectrogram of the RFC sample. The peak on the far right is the biotinylated primer band that was used as a standard to calculate the molecular weights of all other bands. The left side of the spectrogram reveals all three expected cleavage bands (two 10-mers and an 8-mer).

Rosenblum describes new dye labeled terminators for improved DNA sequencing patterns. Figure 1 shows structures of the d rhodamine dye labeled terminators.

Therefore it would have been obvious at the time the invention was made to one of ordinary skill in the art to use the dye label of Rosenblum for the method of Stanton. The motivation is that these dyes show improved spectral resolution and improved brightness compared with the standards dyes used for dye primer sequencing. The total signal is increased. They can be used with advantages in cases when templates molar equivalents are limited.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jezia Riley whose telephone number is 703-305-6855. The examiner can normally be reached on 9:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JEZIA RILEY
PRIMARY EXAMINER

January 29, 2003